Remarks:

With the present amendment, claims 1-6, 9-10, 18, 22-24, 28-31, 43-50, 52, 54, and 58-62 are pending. Claims 2, 4, 6, 11, 29-30, 43-52, 54, and 58-61 have been amended to correct typographical errors and claim dependency. Claims 7, 8, 12-17, 19-21, 25-27, 32-42, 53, 55-57, and 63-70 have been withdrawn from consideration as non-elected subject matter. Applicants respectfully inquire as to the status of claim 61 as it reads on the non-elected species "ENBREL™", yet it was not withdrawn from consideration in the detailed office action. Applicants respectfully assert that no new matter has been added and request entry of said amendments.

The rejection under U.S.C 112 second paragraph should be withdrawn:

The Examiner has rejected claims 1-6, 9-11, 18, 22-24, 28-31, 43-52, 54 and 58-62 based on U.S.C 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner states that the recitation of "immunomodulatory agents" and "immunosuppressive agents" do not apprise the ordinary artisan of the metes and bounds of each of these categories of therapeutic agents. Applicants respectfully disagree and traverse this aspect of the rejection for the following reasons.

The MPEP(8th ed. Aug 2001), 2173.05(a) states:

> The meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application is filed. Applicants need not confine themselves to the terminology used in the prior art, but are required to make clear and precise the terms that are used to define the invention whereby the metes and bounds of the claimed invention can be ascertained. During patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification. *In re Morris*, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969). When the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989).

Applicants respectfully submit that the specification discloses and defines the term "immunomodulatory agents" (see para. 75, 189, 190, and 191 in the instant specification) in sufficient detail to apprise the ordinary artisan of the metes and bounds of this term as recited in the claims. In addition, Applicants respectfully submit that the teachings of the instant specification with respect to "immunomodulatory agents" are aligned with the common terminology utilized by ordinary artisans skilled in the art. Furthermore, acting as their own lexicographer, Applicants have defined "immunomodulatory agents" as an agent that could affect the immune response. The direction of modulation an agent may take is set forth in the description as either immunostimulatory or immunosuppressive, depending on the specific embodiment. For many different conditions, it is well understood in the art which mode the therapy would need to shift the immune response towards. For example, in treating cancer, the desired direction of the immune response may be immunostimulatory, directed at the tumor. In another condition such as an autoimmune disorder, the direction of the immune response may be immunosuppressive. Applicants respectfully submit that one of ordinary skill in the art would appreciate the direction of modulating the immune response based on the condition requiring treatment.

The Examiner further maintains that the recitation of "VITAXIN™" and "REMICADE™" are indefinite because their characteristics are not known.

Applicants respectfully disagree and traverse this aspect of the rejection, and will demonstrate that the terms "VITAXIN™" and "REMICADE™" are definitive and well-defined in the art. At the time of filing, anti-TNFα antibodies, exemplified by REMICADE™, was well known in the art and described throughout the instant specification (see para. 29, 33, 34, and 40). Applicants also note that the USAN term, infliximab, assigned to "REMICADE™" is used throughout the instant specification, demonstrating the art accepted recognition of the molecule named "REMICADE™" at the time of filing. The USAN (United States Adopted Name) council was established to 'serve the health professions in the United States by selecting simple, informative, and unique nonproprietary names for drugs by establishing logical nomenclature classifications based on pharmacological and/or chemical relationships.' In the application for USAN name assignment, the compound must be

described in detail, including a chemical structure, a reference to an IND submission, and a CAS (Chemical Abstract Service) Registry number. The CAS Registry number is a unique identifier that is assigned to compounds based on their structure. For the term "VITAXIN™", Applicants respectfully submit that there is adequate disclosure in the instant specification defining "VITAXIN™" as MEDI-522 and having specific properties such as binding to human integrin αvβ3 (see para. 32 of the instant specification). Furthermore, Applicants respectfully submit that "VITAXIN™" was a term understood in the art as defined by Wu *et al.*, 1998, *PNAS* USA 95(11):6037-6042; International Publication No. WO 90/33919 and WO 00/78815; and U.S. Patent No. 5,753,230, as cited in the instant specification. Nevertheless, in order to expedite prosecution, Applicants amended claims 2, 4, 5, 52, 58, 59 and paragraph [0011] to reflect the assignment of a USAN name for VITAXIN™, etaracizumab. Therefore, the term VITAXIN™ is definite.

Finally, the Examiner maintains that the recitation of trade names "VITAXIN™", "REMICADE™" and "ENBREL™" are indefinite as the formula or characteristics of the product may change over time.

The Applicants respectfully disagree and traverse this aspect of the rejection and will demonstrate that the terms "VITAXIN™", "REMICADE™", and "ENBREL™" are definitive in lieu of the instant specification. The definiteness of the terms "VITAXIN™" and "REMICADE™" have been argued above. Applicants respectfully point out that throughout the specification, soluble TNFα receptors, exemplified by the term "ENBREL™" are described (see para. 29, 32, 33, and 34 of the instant specification). Furthermore, the USAN name, etanercept, assigned to "ENBREL™" is used throughout the instant specification, demonstrating the art accepted recognition of "ENBREL™" at the time of filing. The USAN designations are based on specific characteristics of the named molecules such as molecular weight, structure, and stereochemistry all of which are unique.

However, in the interest of expedient prosecution, Applicants have amended the claims to include generic terminology as the Examiner has requested. Applicants assert that the claims in this amendment are in condition for allowance and

respectfully request that the Examiners objections to the aforementioned claims under 112 second paragraph be withdrawn.

The rejection under U.S.C. 112 first paragraph should be withdrawn:

The Examiner has rejected claims 2, 4, 6, 9-11, 18, 22-24, 28-31, 43-46-54, and 58-62 as containing subject matter which was allegedly not enabled. The Examiner has identified the antibodies "VITAXIN™" and "REMICADE™" as required to practice the invention, yet maintains that an amendment to the specification is required to demonstrate the availability of these components to the general public.

The MPEP(8th ed. Aug 2001), 2404(b) states:

> Biological material need not be deposited unless access to such material is necessary for the satisfaction of the statutory requirements for patentability under **35 U.S.C. 112**. If a deposit is necessary, it shall be acceptable if made in accordance with these regulations. Biological material need not be deposited, *inter alia*, if it is known and readily available to the public or can be made or isolated without undue experimentation. Once deposited in a depository complying with these regulations, a biological material will be considered to be readily available even though some requirement of law or regulation of the United States or of the country in which the depository institution is located permits access to the material only under conditions imposed for safety, public health or similar reasons.

Applicants respectfully submit that "VITAXIN™", "REMICADE™" and the non elected "ENBREL™" were well defined in the literature and readily available to the public at the time of filing of the instant specification.

The MPEP(8th ed. Aug 2001), 608.01(v) states:

> Names used in trade are permissible in patent applications if:
>
> (A) Their meanings are established by an accompanying definition which is sufficiently precise and definite to be made a part of a claim, or
>
> (B) In this country, their meanings are well-known and satisfactorily defined in the literature.

> Condition (A) or (B) must be met at the time of filing of the complete application.

For the reasons outlined above, all of the aforementioned components were committed to the public in advance of the filing as exemplified by the references for "VITAXIN™", and the generic terms infliximab for "REMICADE™" and etanercept for "ENBREL™". Applicants respectfully assert that neither an ATCC submission receipt nor a declaration is required to alleviate the Examiner's rejection. The components "VITAXIN™", "REMICADE™" and "ENBREL™" were well understood in the art and therefore, the Applicants respectfully request that the rejection under U.S.C 112 first paragraph be withdrawn.

The rejection under U.S.C 103(a) should be withdrawn:

The Examiner has rejected claims 1-6, 9-11, 22-24, 28-31, 43-52, 54, and 58-62 as being unpatentable over Feldman et al (U.S. Patent No. 6,270,755) in view of Huse (U.S. Patent No. 5,596,850), The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers *et al.*, Merck Research Laboratories, Whitehouse Station, NJ, 1999 (pg 416-423) and Strom *et al.* (in Therapeutic Immunology edited by Austen *et al.*, Blackwell Science, Cambridge, MA, 1996 (pg 451-456). Applicants respectfully disagree with traverse to this rejection for the following reasons.

The MPEP(8th ed. Aug 2001), 2143 states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Applicants respectfully submit that there is no motivation in the primary references to modify or to combine specific treatment regimes including the combinations taught in the instant specification. Furthermore, the teachings of the

references do not suggest all of the claim limitations as exemplified by the immunomodulation taught in the instant specification (see para. 189-203 of the instant specification). Applicants have defined immunomodulatory agents as compounds that could either be immunosuppressive or immunostimulatory to the immune response.

Teachings of the Cited References

Feldman *et al.*

Feldman *et al.*, teaches the use of anti-TNFα antibodies, including cA2 (REMICADE™) as well as various recombinant forms of antibodies (see columns 7-16) in combination with methotrexate (see columns 18-20) in various dosing scenarios in order to maintain the reduction or elimination of signs associated with a particular TNFα mediated disease (see columns 18-20).

The cited patent only teaches that one skilled in the art could practice the Feldman invention for immunosuppression. It does not provide teachings for scenarios where one skilled in the art would require immunostimulation with a combination therapy. More specifically, Feldman *et al.* is limited in its scope as it only teaches the combination of anti-TNFα antibody therapy with methotrexate and does not support the use of many other immunomodulatory agents that are available, such as the agents described in the specification (see para. 189 – 203 of the instant specification). Feldman also does not teach or suggest that one could target integrins, through an antagonist, in combination with methotrexate or standard therapies to alleviate the signs of a TNFα mediated disease (see abstract para. 11-17 of the instant specification). Feldman is also deficient by containing no teaching of targeting adhesion, migration, or angiogenesis, known physiological properties influenced by $\alpha_v\beta_3$ integrins in order to treat a TNFα mediated disease.

Huse

Huse does not cure the above deficiencies of the Feldman *et al.* patent. Huse does not teach the specific combination of therapies, or the specific immunomodulatory agents as described and claimed in the instant specification (see para. 189 – 203 of the instant specification).

The Secondary References

The secondary references cited by the Examiner (The Merck Manual pages 416-423, and Strom *et al.* pages 451-456) when combined with Feldman *et al.* and Huse also fail to obviate the present invention. These references relate to conventional immunosuppressive therapy, including non-steroidal inflammatory drugs, salicylates, methotrexate and corticosteroids (see Merck pages 419-423, Strom *et al.* pages 451-456), but does not point the skilled artisan to the particular claimed combinations. Furthermore, Strom *et al.* teaches immunosuppressive therapy during organ transplantation, a condition independent of the teaching of the instant specification. As such, the secondary references add little to the teachings of Feldman *et al.* and Huse.

The Combination of References

None of the cited references teach or suggest an $\alpha_v\beta_3$ antagonist in combination with an immunomodulatory agent to alter an immune response characterized by an autoimmune or inflammatory disorder as presently claimed. Indeed, the Examiner acknowledges that 'Feldman *et al.* differs from the claimed methods by not describing all of the current methods of treating rheumatoid arthritis as referenced herein by the Merck Manual, as well as the use of alphavbeta3-specific antibodies in the treatment of rheumatoid arthritis' (see page 7, 4th paragraph of the detailed office action). Applicants respectfully assert that it would not have been obvious to one skilled in the art to identify targeting $\alpha_v\beta_3$ with antagonists in combination with immunomodulatory agents to alter an autoimmune or inflammatory response as claimed.

In further support of this rejection, the Examiner has also cited the MPEP(8th ed. Aug 2001), 2144.06 which states:

> It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

The Applicants respectfully assert that, at the time of filing, no reasonable expectation of success for the teachings of the claimed invention were evident from the cited references. Specifically, the references to dosing regimes in the cited references for combinatorial therapies do not account for the diversity of $\alpha_v\beta_3$ antagonists (see para. 125-128 of the instant specification) exemplified by the claimed invention as they would differ greatly based on their individual chemical characteristics. Therefore, one of skill in the art would not have found it obvious to combine $\alpha_v\beta_3$ antagonists with immunomodulatory agents to alter an immune response.

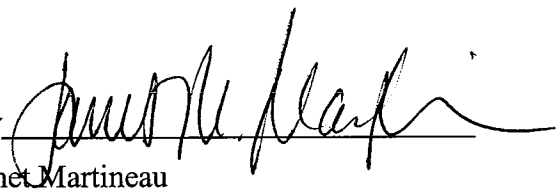
Applicants respectfully assert that there is no motivation from the primary or secondary references to combine or alter teachings to render the current invention obvious. Secondly, Applicants maintain that, at the time of filing, it would not have been obvious to one skilled in the art to combine $\alpha_v\beta_3$ antagonists with immunomodulatory agents to alter an immune response. Finally, Applicants affirm, as argued above, at the time of filing the teachings of the references in part, or as a whole, do not encompass the scope of $\alpha_v\beta_3$ antagonists and immunomodulatory agents and therefore fail to support a *prima facie* case of obviousness.

Conclusions:

Applicants submit a marked up version of the claim set correcting the indefinite claim identifiers to reflect the current prosecution as requested by the Examiner in the outstanding office action. Furthermore, Applicants have amended the claims to correct any typographical errors, including spelling and Trademarks as requested by the Examiner. The claim set submitted herewith also includes corrections to the indefinite claim dependency of the previous claim set.

Applicants respectfully request that the remarks of the present Response be entered and made of record in the present application. The application is believed to be in condition for allowance. Early notice to that effect is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution, the undersigned can be reached at the telephone number indicated below. If any additional fees are required in connection with this paper, please charge Deposit Account No. 500479 for the appropriate amount.

Respectfully submitted,

By 

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